DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 19, 2008 has been entered. Claim(s) 1, 3-6, 10-12, and 20-23 are pending.

Claim Interpretation

As a follow-up to the interview held on May 8, 2008 with Applicant's representatives John R. Van Amsterdam, Ph. D. and Nina White, Applicant is again advised of the broad nature of the claimed invention. First, with regard to the "sorting" step, neither the claimed invention nor specification provide a limiting definition of the step that actively requires an actual physical step. In other words, the "sorting" step is of such a broad nature that it encompasses simply "mentally characterizing" a patient's result as "positive" or "negative" for a "high risk" of cervical cancer.

Next, with regard to the phrase "positive for expression," again neither the claimed invention nor specification provide a limiting definition of the phrase that requires a certain gene expression criteria be met. In other words, in the case of

the instant invention, the measuring of expression of mRNA transcripts can be done by quantifying "copy number," for example. The above phrase does not define a certain "copy number" as positive for expression of the gene. Thus, any detectable amount of gene expression can be considered a positive result.

Lastly, with regard to the phrases "high risk" and "no detectable risk," again neither the claimed invention nor specification provide a limiting definition of the phrases that require a certain risk criteria be met. In other words, the term "high risk" does not require, for example, a correlated level of gene expression, percentage of risk for disease development, or any comparison of assay results. Thus, a patient exhibiting any detectable amount of gene expression can be considered "high risk" for disease development.

When in combination with each other, the above claim interpretations allow for the liberal application of prior art. In other words, any reference teaching or suggesting even the slightest correlation between the expression of the claimed gene and disease development would provide, at the very least, the requisite motivation for a skilled artisan to measure such gene expression as an indicator of the risk of developing the disease.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which

said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claim(s) 1, 3-6, 20, 22, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (WO 99/29890 A2; 17 June 1999).

With regard to claim(s) 1, 2, 22, and 23, Lorincz teaches methods for assessing the risk of a patient with HPV to develop an HPV-based disease, e.g. the risk of a patient with HPV to develop malignant cancer (pg. 4, lines 20-30, for example). Lorincz expressly teaches an embodiment of the invention that involves the measurement of the level of expression of one or more HPV genes discovered to be related to the stage and nature of HP-based disease (e.g. HPV E6, E7, L1, and E2) (pg. 8; example 2 illustrates quantitation HPV mRNA including E6/E7 mRNA; fig. 1,2, for example). More specifically, the reference teaches an in vitro (pg. 11-19; example 2, for example method comprising: screening subjects (pg. 18, cell samples, for example) for expression of mRNA transcripts of the E6 gene of HPV (example 2, for example); wherein the screening for E6 mRNA expression is carried out using isothermal amplification, such as NASBA (pg. 13, for example).

With specific regard to assessing individuals "risk" of developing cervical cancer based on the expression of E6 transcripts, Lorincz expressly teaches that HPV 16 and 18 are predominantly found in cancers (pg. 1-4, 7,13, for example). The reference further teaches that increased expression level of the E6 gene is a

consistent characteristic of high-grade intraepithelial neoplasia and cancers (pg. 3, lines 1-10, for example). The reference further provides a table that classifies certain medical characteristics and HPV-based disease states with expression level of the E6 gene (pg. 8-9, table 1, for example).

With regard to claim(s) 3 and 13, Lorincz teaches NASBA (pg. 13, for example).

With regard to claim(s) 5, 15, and 16, Lorincz teaches tissue from subjects known to have malignant cervical deposits (pg. 15-16,18,23, for example).

With regard to claim(s) 7-9 and 17-19, Lorincz teaches the detection of HPV 16 (pg. 23, for example).

With regard to the above claims, Lorincz does not expressly teach a specific example of "sorting" individuals into cervical cancer development risk categories based on the expression of the E6 gene; however, as stated above, the "sorting" step is of such a broad nature that it encompasses simply "mentally characterizing" a patient's result as "positive" or "negative" for a "high risk" of cervical cancer. Furthermore, the claim does not require a certain gene expression criteria or certain risk criteria be met. Moreover, as outlined above, Lorincz expressly teaches that the prior art recognized: 1) HPV 16 and 18 are predominantly found in cancers; and 2) an increased level of HPV E6 mRNA expression is found in cervical cancers.

Thus, in summary, given the teachings of Lorincz and the broad nature of the claimed invention, it is submitted that it would have been *prima facie* obvious to a skilled artisan at the time of invention to simply screen human subjects for

any detectable level of expression of mRNA transcripts of the E6 gene of HPV 16 and "sort" them as having a "risk" for developing cervical cancer upon the "positive" detection of expression of the E6 gene, and "no risk" given the lack of expression.

With regard to claim(s) 20, as outlined above, Lorincz teaches that HPV 16 and 18 are predominantly found in cancers (pg. 1-4, 7,13, for example). Thus, given the teachings of Lorincz and the broad nature of the claimed invention, it would have been *prima facie* obvious to a skilled artisan at the time of invention to screen human subjects for the expression of mRNA transcripts of the E6 gene of HPV 18, in addition to that of HPV 16.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

Applicant continues to maintain that Lorincz does not teach or suggest a specific relationship between HPV E6 mRNA and high risk for development of cervical carcinoma, asserting that Lorincz would not give a skilled person a reason to measure expression of any particular gene, let alone E6 specifically, and to use the presence of the expression of E6 to classify a person as high risk for development of cervical carcinoma. Given the teachings of Lorincz in combination with the breadth of the claimed invention, the examiner respectfully disagrees. As outlined above, the "sorting" step is of such a broad nature that it encompasses simply "mentally characterizing" a patient's result as "positive" or

"negative" for a "high risk" of cervical cancer. Furthermore, the claim does not require a certain gene expression criteria or certain risk criteria be met. Moreover, as outlined above, Lorincz expressly teaches that the prior art recognized: 1) HPV 16 and 18 are predominantly found in cancers; and 2) an increased level of HPV E6 mRNA expression is found in cervical cancers. Thus, it would have been *prima facie* obvious to a skilled artisan at the time of invention to simply screen human subjects for any detectable level of expression of mRNA transcripts of the E6 gene of HPV 16 and "sort" them as having a "risk" for developing cervical cancer upon the "positive" detection of expression of the E6 gene, and "no risk" given the lack of expression.

With specific regard to Applicant's arguments on page 8, the examiner continues to maintain that Lorincz envisions making HPV-based disease determinations based solely on the expression of E6 mRNA (pg. 8, expression of one or more genes, HPV E6, for example). Lorincz does make reference to comparing expression of HPV genes to non-HPV reference genes (pg. 8, tubulin, cyclin, etc., for example); however, the examiner considers this embodiment a determination based solely on the HPV gene, in the context of the art. As understood by the examiner, mRNA expression assays must include, at the very least, the expression measurement of a control gene (e.g. tubulin), in addition to the gene of interest (e.g. HPV E6), for the assay to provide reliable, accurate results.

Thus, the rejection is maintained.

2. Claim(s) 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (WO 99/29890 A2; 17 June 1999) as applied to claim 1, and in further view of Hendricks et al. (U.S. 5,580,970).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach detection of the E6 gene of HPV type 52.

It is submitted that it was well known in the art at the time of invention that HPV 52 is associated with cervical neoplasia as demonstrated by Hendricks (col. 1, lines 15-45, 60-65, for example).

Thus, it would have been *prima facie* obvious to a skilled artisan at the time of invention to screen human subjects for the expression of mRNA transcripts of the E6 gene of HPV 52, in addition to that of HPV 16.

Response to Arguments

Applicant's arguments have been addressed in the response(s) set forth above.

Conclusion

Claim(s) 1, 3-6, and 20-23 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

/Christopher M. Babic/
Patent Examiner
Art Unit 1637
Technology Center 1600